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Tooth loss is associated with increased risk of total death and death from upper gastrointestinal cancer, heart disease, and stroke in a Chinese population-based cohort

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Background Tooth loss has previously been associated with a higher risk of cancer, heart disease, and stroke, but the role of confounding by smoking remains an issue.

Methods We conducted a cohort study including 29 584 healthy, rural Chinese adults who were participants in a chemoprevention trial from 1986 through 1991 and who have been followed-up through 2001. We categorized tooth loss for each subject as less than or equal to or greater than the median number of teeth lost for other subjects of the same age at baseline. Mortality outcomes were categorized as follows: total death ($n = 9362$), upper gastrointestinal (GI) cancer death ($n = 2625$), other cancer death ($n = 514$), heart disease death ($n = 1932$), and fatal stroke ($n = 2866$).

Results Individuals with greater than the age-specific median number of teeth lost had statistically significant 13% increased risk of total death [95% confidence interval (CI) 9–18%], 35% increased risk of upper GI cancer death (95% CI 14–59%), 28% increased risk of heart disease death (95% CI 17–40%), and 12% increased risk of stroke death (95% CI 2–23%), but no significantly increased risk of death from cancer at other sites. These elevated risks were present in male smokers, male non-smokers, and females, nearly all never-smokers.

Conclusions In this Asian population, tooth loss significantly increased the risk of total death and death from upper GI cancer, heart disease, and stroke. These associations were not limited to tobacco smokers.

Keywords Death, gastrointestinal neoplasms, heart diseases, cerebrovascular accident, tooth loss, cohort studies, China

Several recent longitudinal studies have reported an association between various markers of periodontal disease and heart disease.[1] The association between periodontal disease and stroke has also been examined.[2] Although a majority of these studies found a positive association between poor oral health and cardiovascular diseases, study limitations have raised questions regarding the nature of this association. Specifically, authors have raised concerns that rather than periodontal disease being a true risk factor, the findings are due to the inadequate measurement of and control for tobacco smoking history.[3] Since smoking is strongly correlated with both periodontal and heart disease, residual confounding could produce falsely elevated risk estimates. In addition, several authors have cited the imprecision and subjective nature of the measurements used to assess oral health and periodontal disease as limitations of previously published reports.[1,2] Nearly all of the published studies have examined the US population, with single reports from Canada, Finland, and Germany. Thus,

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no information exists on the association between oral hygiene and these causes of mortality in non-Western populations.

The literature evaluating a potential association between oral health and cancer is sparse. Most reports have focused on associations between oral health and oral cancer.[4,5] The majority have found a significant association after adjustment for use of tobacco and alcohol. Studies from China,[6] Germany,[7] Japan,[8] and Turkey[9] which examined tooth loss and gastric or oesophageal cancer have also reported increased risk associated with poor oral health and/or hygiene. Previously, we reported an association between tooth loss and risk of upper gastrointestinal (GI) cancers in a Chinese cohort.[10]

Linxian, a mostly rural county in north-central China, with a population of approximately 1 000 000, has some of the highest rates of oesophageal and gastric cardia cancer in the world in addition to high rates of stroke. Approximately 85% of all cancer deaths and 28% of total deaths are due to a combination of oesophageal and gastric cancers. Most people in Linxian eat little meat, have low body mass index (BMI), and have low cholesterol. This population has a number of borderline nutritional deficiencies, including most vitamins and minerals. Smoking is restricted to men, but about 33% of males have never smoked. These characteristics distinguish the Linxian population from previously studied Western populations, and may make it more representative of populations in the developing world.

Since 1985 we have been studying a cohort of 29 584 individuals from Linxian, People's Republic of China. Originally, these individuals were recruited as subjects in a randomized placebo-controlled trial called the General Population Trial. The trial lasted from 1986 to 91 and tested the effects of vitamin and mineral supplementation on oesophageal and gastric cancer incidence and mortality, and mortality due to other causes. The design, conduct, and results of that trial have been reported.[11–13] In the current study, we examine the associations between tooth loss and total death, upper GI cancer death, other cancer death, heart disease death, and stroke death in this cohort of individuals from the General Population Trial over the 15 year period 1986–2001.

Methods

Cohort population and variable definition

The Nutrition Intervention Trial General Population Trial design and methods have been reported.[14] The General Population Trial cohort consists of 29 584 subjects aged 40–69 at baseline who were recruited from four communes. Sixty one per cent of the eligible participants enrolled in the trial and took part in the baseline screening exam. At the time of study recruitment, March–May 1985, subjects completed a questionnaire and received a brief physical examination. As part of this baseline interview, subjects received an oral exam and trial participants were asked if they had lost any permanent teeth. Interviewers then counted the number of remaining teeth in all those who reported missing teeth. Those subjects who reported no missing teeth were assumed to have 32 teeth. We excluded subjects without data for number of teeth lost at baseline, 2.4% of the cohort.

Other information collected at the baseline interview and examination included age, sex, height, weight, tobacco consumption (current smoking, past smoking, age of commencement, age of cessation, and typical intensity for both cigarette and pipe tobacco), ethanol consumption, and systolic and diastolic blood pressure.

Throughout the 15 years of follow-up, cancer incidence and cause-specific mortality was ascertained on a monthly basis by village doctors. Mortality was classified into one of 61 categories used by Chinese physicians at the start of the trial. During the 5.25 years of the trial, each subject was contacted monthly by the village doctor. In the 10 years subsequent to the end of the trial, information on the incident cancers and causes of death of our subjects have been obtained each month from the records of the village doctors. Periodically, medical records have been reviewed at all medical facilities in Linxian and the Cancer Hospital in the prefecture capital of Anyang. In 1991, 1996, and 2001 all living cohort members were interviewed and examined. Since the initiation of the trial all diagnoses of incident and fatal cancers have been reviewed by a panel of experts. Through the 1996 follow-up this consisted of both Chinese and US experts. Subsequent to 1996 the review has been by Chinese experts alone. There is confirmatory diagnostic material (e.g. X-rays, cytology, histology) for approximately 90% of the cancers. Throughout the study the non-cancer deaths reported by the village doctors have been reviewed by senior Chinese clinicians. Most of these diagnoses are based on clinical histories.

In this study, we examine the association of tooth loss with all deaths, and the cause-specific categories deaths from upper GI cancer, heart disease, stroke, and other cancer. These categories account for 85% of all the deaths. Only two other causes of death exceeded 2% of all deaths, accidents ($n = 370$) and liver cirrhosis ($n = 194$). Deaths due to oesophageal, gastric cardia, and non-cardia gastric cancers (hereafter upper GI cancer) accounted for 51%, 23%, and 10% of total cancer deaths, respectively. The remaining 16% of cancer deaths were mainly liver, lung, and colorectal cancers. We separated the upper GI cancer deaths from the others because: (i) we previously observed an association between upper GI cancer deaths and tooth loss based on the first 5.25 years of follow-up of this cohort; (ii) the risks were similar between individual upper GI sites[10]; and (iii) since this group represents the vast majority of cancer deaths, it would determine any associations with a total cancer outcome.

Ninety-five per cent of heart disease deaths were originally classified into five categories: congestive heart failure (50%), ischaemic heart disease (18%), hypertensive heart disease (16%), or other circulatory problems (10%). Since there is both clinical and aetiologic overlap in these categories we combined them into one category. The other 5% included rheumatic heart disease (5%) or congenital heart disease (<1%). These we also included in the heart disease category.

Stroke death included all cerebrovascular events. Advanced imaging techniques were not widely available in rural China and autopsies are rarely performed, due to social mores, so we could not distinguish between haemorrhagic and ischaemic strokes. Population statistics in China indicate that approximately two-thirds of the strokes are ischaemic.[15] In 1994 we independently assembled several hundred clinical histories of deaths classified by the village doctors as stroke and found all to be consistent with that diagnosis.

Follow-up time was calculated as days from the start of intervention in May 1986 until the day of death or though May 2001. A small number of the cohort was lost to follow-up ($n = 244$, 0.85%) and those individuals were censored at the last time their vital status was known.

Statistical methods

There was a strong positive association between tooth loss and age with $R^2 = 0.26$.[10] There was also a strong positive association between age and risk of death for each of our outcome variables. Using either ordinary least squares or loess regression we found that the tooth loss distributions were asymmetric and heteroscedastic around the regression means. This persisted despite higher order polynomial terms and variable transformation. Consequently, we estimated the median tooth loss at each age by a loess smooth of age-specific medians. The median number of subjects was 489 for each year of age used in creating these cut-offs. The optimal neighbourhood size for smoothing was chosen using cross-validation.[16] We classified individuals into two categories depending upon whether their tooth loss was greater than the loess predicted median for their age. This dichotomous variable was used as the exposure measure to estimate the association of tooth loss with other baseline covariates, as well as the association of tooth loss with mortality outcomes. We estimated the former using logistic regression and the latter using the Cox proportional hazards (CPH) models described below.

We built parsimonious CPH models for all outcomes by testing the addition of age, sex, smoking, drinking, height, weight, and systolic blood pressure and only included those variables that changed the beta coefficient for tooth loss. Given the potential importance of smoking as a confounder, we tested different parameterizations of tobacco use and found no material changes in the risk estimates with either duration, intensity, or cumulative use (duration × intensity), so we retained ever-smoking ⩾6 months as our exposure variable. We sequentially tested for effect modification of the tooth loss-mortality associations by adding interactions terms between tooth loss and age, smoking status, and sex. Since only 0.23% of women were ever-smokers, we put forward separate risk estimates for females, never-smoking males, and ever-smoking males for the outcomes in which smoking was an effect modifier. We used models that allowed time-dependent relative risks (RRs) to test for deviations from the proportionality assumption. No such deviations were detected. All *P*-values are from two-sided likelihood ratio tests comparing nested models. Values <0.05 are considered statistically significant. Statistical analyses were conducted using SAS software (SAS Institute, Cary, NC) and Epicure (HiroSoft International, Seattle, WA).

Results

Overall, cohort members who died during the 15 year follow-up period were older, more likely male, more likely smokers, had higher systolic blood pressure, and had more lost teeth than the cohort as a whole (all $P < 0.0001$) (Table 1). Any tooth loss was reported by 74% of the cohort. The median number of teeth lost [interquartile range (IQR)] was 7 (1–16) for females

Table 1 Analytic cohort[a] characteristics at baseline[b] overall and by cause-specific mortality in the Nutrition Intervention Trial General Population Trial Cohort, Linxian, PRC, 1986–2001

Variable	Total cohort	Total death	Upper GI cancer	Other cancer	Heart disease	Stroke	Other Death
Number	28 790	9362	2625	514	1932	2866	1425
Age, years median (IQR[c])	52 (44–59)	59 (53–64)	57 (51–62)	56 (50–61)	61 (56–66)	60 (54–64)	59 (51–64)
Sex, % female	55.0	46.4	43.9	41.4	46.3	51.4	43.2
Smoking[d], % ever	30.3	37.7	41.3	42.2	39.2	32.2	38.4
Males, % yes	67.1	70.0	73.3	71.8	72.3	66.0	67.3
Females, % yes	0.23	0.48	0.52	0.47	0.89	0.27	0.33
Drinking[e],% yes	23.8	21.5	23.2	27.4	20.3	18.7	23.4
Height, m median (IQR)	1.5	1.5	1.5	1.6	1.5	1.5	1.5
	(1.5–1.6)	(1.5–1.6)	(1.5–1.6)	(1.5–1.6)	(1.5–1.6)	(1.5–1.6)	(1.5–1.6)
Weight, kg median (IQR)	55 (50–60)	55 (50–60)	55 (50–60)	56 (52–60)	54 (48–59)	55 (50–60)	54 (49–59)
BMI, kg/m^2 median (IQR)	23.0 (21.3–24.8)	22.7 (21.1–24.5)	22.7 (21.1–24.1)	22.7 (21.4–24.6)	22. (20.7–24.4)	23.1 (20.0–23.1)	22.7 (20.9–24.2)
Systolic BP, mm Hg median (IQR)	126 (110–145)	140 (120–160)	130 (110–150)	130 (114–145)	140 (123–160)	150 (134–175)	130 (115–150)
Any lost teeth, % yes	74.2	85.1	83.7	77.2	88.9	85.8	83.7
Teeth lost, median(IQR)	6 (0–15)	10 (4–22)	9 (3–20)	7 (1–17)	13 (5–25)	10 (4–23)	10 (4–23)

[a] Excludes individuals missing data on tooth loss, 2.4% of the original cohort.

[b] All characteristics describe the outcome groups at the time of the baseline interview, May 1985, not at the time of death.

[c] Interquartile range (25th–75th percentile).

[d] Ever-smoking is defined as ever consuming tobacco for ⩾6 months.

[e] Drinking is defined as intake of any ethanol in the previous 12 months.

and 5 (0–12) for males. Smoking was essentially limited to males with 0.23% of females being ever-smokers. Among male smokers, the median IQR was 10 (7–20) cigarettes smoked per day, 27 (19–36) years total duration of smoking, and 15.5 (7.8–25) cumulative pack-years.

In our prior analysis we examined whether age, sex, smoking, drinking, measures of overall health status, and intake of certain foods were associated with the number of teeth lost.[10]

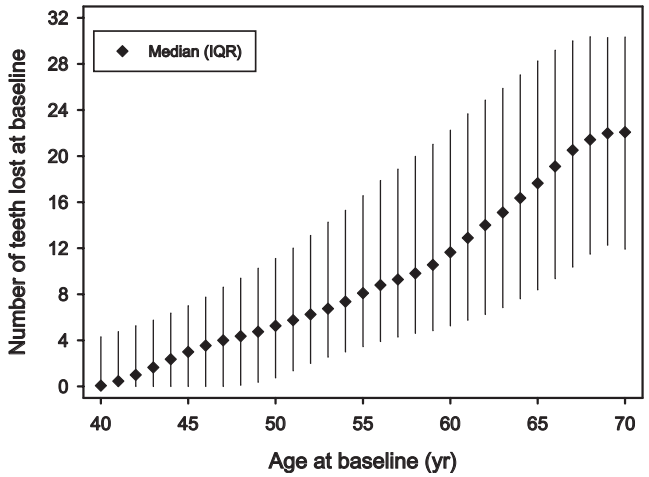

Figure 1. Median tooth loss and IQR (25th–75th percentile) for tooth loss by age at baseline in the Nutrition Intervention Trials General Population Trial cohort. Age-specific medians and quartiles were estimated using loess regression as described in the Methods section. This distribution was used to define exposure to tooth loss for our risk calculations. Individuals above the median for tooth loss for subjects of the same age at baseline were considered exposed

Age was the only variable that explained a substantial proportion of the total variability (R^2 = 0.26). Figure 1 is a graph of the median number of teeth lost vs the age at baseline. With increasing age, cohort members showed increases in both the median number of teeth lost and variation in the number of teeth lost. To adjust for this dependency of tooth loss on age, we created a dichotomous tooth loss variable based on whether an individual's tooth loss was greater than the median for cohort subjects of the same age. We used logistic regression to examine the strength of the association between the dichotomous tooth loss variable and the variables in Table 1. We found that the odds of tooth loss were lower in non-smoking males than in females odds ratio (OR) 0.47 (95% CI 0.43–0.50). Among males, smoking increased the risk of tooth loss by 35%, OR 1.35 (95% CI 1.25–1.46). Drinking was not an important predictor of tooth loss. Neither were indicators of general health, such as illness which precludes work or the number of colds in the previous 12 months, among others. None of the 15 different food types examined was associated with tooth loss, but minimal variation in food consumption reduces the ability to detect the association between the diet and other factors.

Table 2 presents the RR (95% CI) of total and cause-specific mortality for age (by decade), sex, and ever-smoking. Age and being male were significant risk factors for all outcomes. Age conferred the greatest increased risk for heart disease, RR 4.11 per decade. Ever-smoking was associated with increased risk of total, upper GI cancer, and heart disease mortality, but the risk elevations were more modest than those associated with age.

Table 3 presents the RR for total and cause-specific mortality by tooth loss. We found that individuals with greater than the age-specific median number of teeth lost had statistically significant increases in total mortality and mortality from upper

Table 2 Associations between age, sex, and ever-smoking and cause-specific mortality in the General Population Trial Cohort, Linxian, PRC, 1986–2001

Mortality	Cases	Exposure	RR[a]	95% CI	*P*[b]
Death	9362	Age, 10 years	2.79	2.72–2.86	<0.0001
		Sex, male	1.32	1.24–1.40	<0.0001
		Smoking, ever	1.18	1.11–1.25	<0.0001
Upper GI cancer	2625	Age, 10 years[c]	2.20	2.07–2.35	<0.0001
		Sex, male	1.32	1.18–1.48	<0.0001
		Smoking, ever	1.37	1.22–1.53	<0.0001
Heart Disease	1932	Age, 10 years	4.11	3.86–4.37	<0.0001
		Sex, male	1.22	1.07–1.40	0.0035
		Smoking, ever	1.35	1.18–1.54	<0.0001
Stroke	2866	Age, 10 years	2.58	2.42–2.76	<0.0001
		Sex, male	1.35	1.78–1.54	<0.0001
		Smoking, ever	1.11	0.96–1.28	0.15
Other Cancer	514	Age, 10 years	1.91	1.72–2.12	<0.0001
		Sex, male	1.55	1.20–1.99	0.0010
		Smoking, ever	1.27	0.99–1.64	0.054

[a] The models for total death, upper GI cancer, other cancer, and heart disease were adjusted for age, sex, ever-smoking, and tooth loss. The models for stroke were also adjusted for height, weight, and systolic blood pressure.

[b] All *P*-values came from likelihood ratio tests comparing nested models.

[c] Age interaction RR per 10 years of age = 0.89.

Table 3 The relative risk of tooth loss[a] on total and cause-specific mortality in the General Population trial cohort, Linxian, PRC (1986–2001)

				Relative risk by sex and smoking Status[d]				Smoking interaction	
Mortality	**RR**[b]	**95% CI**	***P***[c]	Smoking	Cases	RR	95% CI	*P*	*P*
Death	1.13	1.09–1.18	<0.0001	Females	4346	1.07	1.01–1.14	0.024	
				Male never-smokers	1500	1.09	0.98–1.21	0.14	<0.0001
				Male ever-smokers	3516	1.24	1.16–1.32	4×10^{-10}	
Upper GI cancer	1.35[e]	1.14–1.59	0.0096[f]	Females	1152	1.24	0.98–1.58	0.19	
				Male never smokers	394	1.59	1.03–2.45	0.041	0.0018
				Male ever-smokers	1079	1.39	1.06–1.83	0.0001	
Heart disease	1.28	1.17–1.40	<0.0001	Females	893	1.10	0.96–1.25	0.17	
				Male never-smokers	287	1.57	1.24–1.98	0.0002	0.037
				Male ever smokers	752	1.41	1.23–1.63	2×10^{-6}	
Stroke	1.11	1.01–1.23	0.027		2866				0.54
Other cancer	1.07	0.89–1.28	0.44		514				Not tested

[a] Tooth loss is defined as having greater than the loess smoothed age-specific median number of teeth lost at baseline (see Statistical methods and Figure 1).

[b] The models for total death, upper GI cancer, other cancer, and heart disease were adjusted for age, sex, and ever-smoking. The models for stroke were also adjusted for height, weight, and systolic blood pressure.

[c] All *P*-values came from likelihood ratio tests comparing nested models.

[d] Risks for tooth loss are presented within individual sex-by-smoking stratum when interaction tests indicated that there was a statistically significant difference between the risk from tooth loss in smokers and non-smokers. Since in this cohort only males are smokers, there is no female-smoker category.

[e] Upper GI cancer models include adjustment for an interaction between tooth loss and age at baseline ($P = 0.015$). The relative risk in the table is for individuals who were 40 years. The RR of tooth loss decreases by a factor of 0.89 for each additional 10 years of age. See Results section for the RRs of tooth loss estimated within three separate age strata.

[f] *P*-value for upper GI cancer comes from a 2° of freedom likelihood ratio test where the larger model contains terms for both the main effect of tooth loss and the interaction of tooth loss with age.

GI cancer, heart disease, and stroke. Tooth loss was associated with increased risk of total mortality and stroke mortality by approximately 11%, and upper GI cancer and heart disease mortality by approximately 30%. For total, upper GI cancer, and heart disease mortality the effect of tooth loss was significantly different in smokers and non-smokers. However, the magnitude of these differences in risk did not vary greatly between male never-smokers or male ever-smokers. Regardless of smoking status, tooth loss was associated with an increased risk of mortality. For upper GI cancer and heart disease, risk estimates for tooth loss were higher in male never-smokers than in male ever-smokers.

Age was a significant effect modifier of the upper GI cancer mortality and tooth loss association ($P = 0.015$) with the greatest increased risk in the youngest subjects. There were 547, 1121, and 957 cases of upper GI cancer among subjects <50, 50–59, and ⩾60 years respectively. The RRs were 1.25 (95% CI 1.06–1.48), 1.18 (95% CI 1.05–1.33), and 0.99 (95% CI 0.87–1.13) in these three strata.

Discussion

In this prospective cohort study, we examined the association of tooth loss with total and cause-specific mortality over a 15 year period in approximately 30 000 individuals from rural China. We found that subjects with greater than the age-specific median number of teeth lost had a 13% increased incidence of mortality from any cause. The three most frequent causes of death in this cohort, upper GI cancer, heart disease, and stroke, were elevated by 35%, 28%, and 12%, respectively. For deaths from other cancers, the risk elevation was a statistically insignificant 7%.

Previous studies in Western populations have reported an increased risk of heart disease and stroke in subjects with periodontal disease. In those studies smoking was strongly associated with both the markers of periodontal disease and the causes of death, particularly heart disease deaths, suggesting that the significant associations could be due to residual confounding.[3] In our population we found a positive association between smoking and tooth loss, although the magnitude was smaller than in US studies.[17,18] Several features unique to our study allowed us to separate more precisely the effect of tooth loss in never- and ever-smokers. Nearly 16 000 of our subjects were female, and fewer than 40 had ever smoked tobacco. In females, tooth loss significantly increased the risk of all-cause mortality. Although, when examined separately by sex, the estimates in females tended to be lower than those in males, these differences were generally small. About two-thirds of the male subjects had ever smoked tobacco regularly for more than 6 months. For deaths due to upper GI cancer and heart disease we calculated RRs in never- and ever-smokers separately, and found that the increased risk was greater among never-smoking males. We conclude that given the prospective assessment of smoking, the smoking characteristics of our population, the magnitude of the association of smoking with tooth loss, and the consistency of the direction of the risk estimates in the sub-groups, residual confounding by smoking could not account for the finding that upper GI cancer and heart disease mortality were increased in individuals with greater tooth loss.

A second concern raised in multiple review articles is the subjectivity of the oral health exposure measures used in previous studies.[1,2] Both probing and non-probing indices (e.g. Russell's periodontal index) have been used with different

cut-offs for the presence of periodontal disease, even within the same cohort.[18,19] In our study, we used tooth counts as ascertained by physical examination at study baseline. This measure is objective, and since it was gathered prospectively, uninfluenced by subsequent outcome. Tooth loss is typically the result of trauma, caries, or periodontal disease. We recently conducted a dental health survey in Linxian in which ~600 subjects received comprehensive oral health examinations. In this surveyed group we found that moderate to severe periodontal disease was common, while caries were less common (unpublished data). This suggests that tooth loss, in this population, is primarily due to periodontal disease. The accuracy of this supposition, however, affects only the biological mechanisms we propose below and not the accuracy of the risk estimates we report.

As in any epidemiological study, unmeasured confounders could explain the associations we found between tooth loss and total, upper GI cancer, heart disease, and stroke death. Tooth loss could be a marker for another chronic disease, which is causally associated with each of our outcomes. The subjects in our cohort were originally recruited as participants in a randomized trial, and one eligibility condition required that subjects be free of chronic disease. Therefore, we think it unlikely that diseases detectable by a questionnaire and/or a physical examination gave rise to the associations we report, especially in light of the widespread exposure to tooth loss and the large number of deaths in the cohort. Furthermore, we found no correlation between tooth loss and simple measures of general health, such as the number of colds in the previous 12 months.[10] Inclusion of these variables in the risk models did not alter our results. Tooth loss is also correlated with lower socio-economic status (SES) in the West, suggesting that SES could be a confounder of our tooth loss disease associations. But, our cohort was drawn exclusively from rural villages and ~98% of our subjects reported their occupation as farmer. This homogeneity suggests that confounding by SES is unlikely to explain our results.

Previous studies and reviews have discussed potential causal mechanisms that might explain the association between tooth loss and systemic disease. For upper GI cancer, one potential explanation is that tooth loss might alter the dietary pattern to one that increases the risk of disease. In this population, we saw only very small correlations between tooth loss and diet, making this explanation unlikely. Second, authors have hypothesized that tooth loss would cause individuals to swallow large, poorly chewed boluses of food which might irritate the oesophagus.[20] Since we have no measure of size of food swallowed, or the impact of tooth loss on that size, we cannot directly address this hypothesis. However, in our earlier study of tooth loss and upper GI cancer in this population we found the elevated risk was associated with the first teeth lost, not the last teeth lost. In the current analysis we see the strongest association in younger persons, who have fewer teeth lost. Both findings suggest that increased risk of upper GI cancer occurs prior to the extensive tooth loss that would be required to impair chewing significantly. Finally, we previously found that tooth loss was associated with an increased risk of cancer in the body of the stomach[10], an organ that is unlikely to be affected by the mechanical trauma hypothesis.

The strongest hypothesis relating tooth loss to upper GI cancer is that tooth loss is associated with an oral flora that preferentially produces carcinogenic by-products which increase the risk of upper GI cancer. For example, individuals with tooth loss may have a greater burden of an oral flora that is more effective in the reduction of nitrate to nitrite. This nitrite can then spontaneously react with amines and be converted to carcinogenic nitrosamines.[21] Nair *et al*. demonstrated that poor oral hygiene is associated with increased exposure to nitrosamines[22] and some nitrosamines have been demonstrated to be gastrointestinal organ-specific carcinogens.[23,24] Acetaldehyde and reactive oxygen species are two additional potential carcinogenic metabolites produced by oral bacteria.

For cardiovascular diseases, several potential mechanisms have been proposed in the literature for the increased risk observed in individuals with poor oral health. These include infectious agents collaborating in atheroma formation, indirect effects of chronic inflammation, and common genetic predisposition to periodontal disease and vascular diseases (reviewed[25,26]). We have no direct evidence to support or refute any of these hypotheses but the latter two merit further discussion.

Periodontal disease results from bacterial infection, and the disease severity appears to be modulated by host-responses.[27] The host-response to periodontal infection can lead to systemic exposure to pro-inflammatory cytokines. Host-responses to *Helicobacter pylori*-induced inflammation play a role in gastric cancer.[28] The role of chronic inflammation in oesophageal squamous cell carcinoma, the histological type of oesophageal cancer seen in Linxian, is less clear, but use of nonsteriodal anti-inflammatory drugs (NSAID) has been shown to protect against both oesophageal and gastric cancer.[29] NSAIDs also have protective effects for heart disease.[30] Thus, periodontal disease may increase the risk of both upper GI cancer and heart disease through the chronic release of inflammatory mediators.

Individual responses to inflammation are partially due to genetic variation. As previously noted, upper GI cancer, heart disease, and periodontitis have all been linked to host-responses to inflammation. Thus, it is possible that periodontitis, rather than being the cause of upper GI cancer and heart disease, is a marker for genetic factors which underlay all three diseases.

All previous studies evaluating the association between oral health and cardiovascular disease have been performed in Western populations. Our cohort is quite distinct from Western populations in its dietary habits, lower median BMI and cholesterol, and limited smoking and drinking habits, and, with regard to these characteristics, more representative of populations throughout the developing world. As in most areas of the developing world, this population has had little access to preventive dentistry. Our findings indicate that total mortality and certain specific causes of mortality in the Linxian population are significantly elevated in individuals with periodontal disease, and if causal, suggest that the provision of routine dental care and other dental public health interventions might lead to reductions in early death.

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KEY MESSAGES

- Subjects with greater then the age-specific median tooth loss are at a higher risk of overall death and death from upper GI cancer, heart disease, and stroke in a rural Chinese population
- These associations for upper GI cancer and heart disease were not limited to smokers and were strongest in never-smoking males

References

[1] Genco R, Offenbacher S, Beck J. Periodontal disease and cardiovascular disease: epidemiology and possible mechanisms. *J Am Dent Assoc* 2002;**133** (Suppl.)**:**14S–22S.

[2] Joshipura K. The relationship between oral conditions and ischemic stroke and peripheral vascular disease. *J Am Dent Assoc* 2002;**133** (Suppl.)**:**23S–30S.

[3] Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontitis—systemic disease associations in the presence of smoking—causal or coincidental? *Periodontol* 2000;**30**:51–60.

[4] Bundgaard T, Wildt J, Frydenberg M, Elbrond O, Nielsen JE. Case-control study of squamous cell cancer of the oral cavity in Denmark. *Cancer Causes Control* 1995;**6**:57–67.

[5] Zheng TZ, Boyle P, Hu HF *et al*. Dentition, oral hygiene, and risk of oral cancer: a case-control study in Beijing, People's Republic of China. *Cancer Causes Control* 1990;**1**:235–41.

[6] Wang YP, Han XY, Su W *et al*. Esophageal cancer in Shanxi Province, People's Republic of China: a case-control study in high and moderate risk areas. *Cancer Causes Control* 1992;**3**:107–13.

[7] Wolff G, Lauter J. On epidemiology of gastric cancer. *Arch Geschwulstforsch* 1976;**46**:1–14.

[8] Watabe K, Nishi M, Miyake H, Hirata K. Lifestyle and gastric cancer: a case-control study. *Oncol Rep* 1998;**5**:1191–94.

[9] Demirer T, Icli F, Uzunalimoglu O, Kucuk O. Diet and stomach cancer incidence. A case-control study in Turkey. *Cancer* 1990;**65**:2344–48.

[10] Abnet CC, Qiao Y-L, Mark SD *et al*. Prospective study of tooth loss and incident esophageal and gastric cancers in China. *Cancer Causes Control* 2001;**12**:847–54.

[11] Li JY, Taylor PR, Li B *et al*. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementation, cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst* 1993;**85**:1492–98.

[12] Blot WJ, Li J-Y, Taylor PR *et al*. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;**85**:1483–92.

[13] Blot WJ, Li JY, Taylor PR *et al*. The Linxian trials: mortality rates by vitamin-mineral intervention group. *Am J Clin Nutr* 1995;**62**:1424S–26S.

[14] Li B, Taylor PR, Li J-Y *et al*. Linxian nutrition intervention trials. Design, methods, participant characteristics, and compliance. *Ann Epidemiol* 1993;**3**:577–85.

[15] Shi FL, Hart RG, Sherman DG, Tegeler CH. Stroke in the People's Republic of China. *Stroke* 1989;**20**:1581–85.

[16] Hastie T, Tibshirani R. *Generalized Additive Models*. 1st edn. New York: Chapman and Hall, 1990.

[17] Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J Am Coll Cardiol* 2001;**37**:445–50.

[18] Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. *JAMA* 2000;**284**:1406–10.

[19] Wu T, Trevisan M, Genco RJ *et al*. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Arch Intern Med* 2000;**160**:2749–55.

[20] Yang CS. Research on esophageal cancer in China: a review. *Cancer Res* 1980;**40**:2633–44.

[21] Shapiro KB, Hotchkiss JH, Roe DA. Quantitative relationship between oral nitrate-reducing activity and the endogenous formation of N-nitrosoamino acids in humans. *Food Chem Toxicol* 1991;**29**:751–55.

[22] Nair J, Havovi S, Chakradeo P, Jakhi SA, Bhide SV. Effect of oral hygiene on nitrosamine formation in the mouth. In: O'Neill IK, Bartsch H, (eds). *Nitroso Compounds: Biological Mechanisms, Exposure and Cancer Etiology*. Lyon: International Agency for Research on Cancer, 1992.

[23] Chhabra SK, Souliotis VL, Kyrtopoulos SA, Anderson LM. Nitrosamines, alcohol, and gastrointestinal tract cancer: recent epidemiology and experimentation. *In Vivo* 1996;**10**:265–84.

[24] Magee PN. Nitrosamines and human cancer: introduction and overview. *Eur J Cancer Prev* 1996;**5** (Suppl.)**:**7–10.

[25] Slots J, Kamma JJ. General health risk of periodontal disease. *Int Dent J* 2001;**51**:417–27.

[26] Scannapieco FA, Genco RJ. Association of periodontal infections with atherosclerotic and pulmonary diseases. *J Periodontal Res* 1999;**34**:340–45.

[27] Van Dyke TE, Serhan CN. Resolution of inflammation: a new paradigm for the pathogenesis of periodontal diseases. *J Dent Res* 2003;**82**:82–90.

[28] Correa P. Bacterial infections as a cause of cancer. *J Natl Cancer Inst* 2003;**95**:E-3.

[29] Farrow DC, Vaughan TL, Hansten PD *et al*. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1998;**7**:97–102.

[30] Mehta P. Aspirin in the prophylaxis of coronary artery disease. *Curr Opin Cardiol* 2002;**17**:552–58.

Residents of Linxian (photo: Dr P Taylor)

Family outing in the Peach Blossom Valley near Linzhou (photo: Dr C Abnet)